CLAIMS

What is claimed is:

1.     An isolated nucleic acid which encodes a precursor glucagon-like peptide 1 (GLP-1) comprising mammalian GLP-1 linked to a heterologous signal sequence.

2.     The isolated nucleic acid of Claim 1 wherein the GLP-1 encoded by the nucleic acid has an amino acid sequence of SEQ ID NO: 21.

3.     The isolated nucleic acid of Claim 1 wherein the GLP-1 is a modified GLP-1.

4.     The isolated nucleic acid of Claim 3 wherein the modified GLP-1 encoded by the nucleic acid has an amino acid sequence in which alanine at position 8 is replaced with glycine (SEQ ID NO: 21).

5.     The isolated nucleic acid of Claim 3 wherein the modified GLP-1 encoded by the nucleic acid has an amino acid sequence selected from the group consisting of: GLP-1 (7-34) (SEQ ID NO: 23), GLP-1(7-35) (SEQ ID NO: 24), GLP-1(7-36) (SEQ ID NO: 25), $Val^8$-GLP-1(7-37) (SEQ ID NO: 26), $Gln^9$-GLP-1(7-37) (SEQ ID NO: 27), $Thr^{16}$-$Lys^{18}$-GLP-1(7-37) (SEQ ID NO: 28), and $Lys^{18}$ (SEQ ID NO: 29).

6.     The isolated nucleic acid of Claim 1 wherein the heterologous signal sequence is a sequence selected from the group consisting of: a signal peptide sequence and a leader sequence.

7.     The isolated nucleic acid of Claim 6 wherein the leader sequence is derived from a protein selected from the group consisting of: a cytokine, growth factor, colony stimulating factor, a clotting factor, (PACAP)/Glucagon superfamily and serum protein.

8.     The isolated nucleic acid of Claim 6 wherein the heterologous signal sequence is selected from the group consisting of: a secreted human alkaline phosphatase (SEAP) signal peptide sequence, a proexendin-4 leader sequence, a pro-helodermin leader sequence, a pro-glucose dependent insulinotropic polypeptide (GIP) leader sequence, a

pro-insulin growth factor 1 (IGF1) leader sequence, a preproglucagon leader sequence, an alpha-1 antitrypsin leader sequence and an insulin like growth factor 1.

9. The isolated nucleic acid of Claim 1 wherein the heterologous signal sequence comprises a furin cleavage site.

10. The isolated nucleic acid of Claim 9 wherein the furin cleavage site encodes a peptide selected from the group consisting of: Arg-X-Lys-Arg (SEQ ID NO: 34), Arg-X-Arg-Arg (SEQ ID NO: 35), Lys/Arg-Arg-X-Lys/Arg-Arg (SEQ 1D NO: 36) and Arg-X-X-Arg (SEQ ID NO: 37).

11. The isolated nucleic acid of Claim 1 wherein the heterologous signal sequence comprises a prohormone convertase (PC) cleavage site.

12. The isolated nucleic acid of Claim 1, wherein the nucleic acid is selected from the group consisting of

    a) SEQ ID NO:1;

    b) SEQ ID NO:3;

    c) SEQ ID NO:5;

    d) SEQ ID NO:7;

    e) SEQ ID NO:9;

    f) SEQ ID NO:11;

    g) SEQ ID NO:13;

    h) SEQ ID NO:15;

    i) SEQ ID NO: 17; and

    j) SEQ ID NO:19.

13. The isolated nucleic acid of Claim 1, wherein the precursor GLP-1 has an amino acid sequence selected from the group consisting of:

a) SEQ ID NO:2;

b) SEQ ID NO:4;

c) SEQ ID NO: 6;

d) SEQ ID NO:8;

e) SEQ ID NO:10;

f) SEQ ID NO:12;

g) SEQ ID NO:14;

h) SEQ ID NO:16;

i) SEQ ID NO: 18; and

j) SEQ ID NO: 20.

14.　An isolated polypeptide encoded by a nucleic acid of Claim 12.

15.　An isolated precursor glucagon-like peptide 1 (GLP-1) comprising mammalian GLP-1 linked to a heterologous signal sequence.

16.　An isolated precursor glucagon-like peptide I (GLP-1) of Claim 15, wherein the precursor GLP-1 has an amino acid sequence selected from the group consisting of:

a) SEQ ID NO:2;

b) SEQ ID NO:4;

c) SEQ ID NO:6;

d) SEQ ID NO:8;

e) SEQ ID NO:10;

f) SEQ ID NO:12;

g) SEQ ID NO:14;

h) SEQ ID NO:16;

i) SEQ ID NO:18; and

j) SEQ ID NO: 20.

17.    An expression vector comprising a nucleic acid of Claim 1.

18.    An isolated host cell comprising a nucleic acid of Claim 1.

19.    A method of promoting insulin production in an individual in need thereof, comprising administering to the individual an effective amount of a nucleic acid encoding a precursor glucagon-like peptide 1 (GLP-1) comprising mammalian GLP- I linked to a heterologous signal sequence, wherein the precursor GLP-1 is cleaved *in vivo* or *ex vivo* which results in generation of activated GLP-1 in the individual.

20.    The method of Claim 19 wherein the individual has a blood sugar defect selected from the group consisting of: Type I diabetes and Type II diabetes.

21.    The method of Claim 20 wherein the nucleic acid encoding the precursor GLP-1 is administered in a viral vector.

22.    The method of Claim 20 wherein the nucleic acid encoding the precursor GLP-1 is administered as naked DNA.